REMARKS / ARGUMENTS

The Office Action dated October 27, 2008 has been carefully considered. It is believed that the comments submitted herewith represent a complete response to the Examiner's rejection and place the present application in consideration for allowance. Reconsideration is respectfully requested.

35 USC § 103

The Examiner has rejected claims 12-13, 17, 22 and 50-53 as being unpatentable over Jaleco et al. (2001, J. Exp. Med. 194:991-1001, IDS); Nakano et al. (1994, Science 265:5157 IDS); Pui et al. (Immunity, 1999, 11:299-308), and Tatsumi et al. (1990, Proc. Natl. Acad. Sci. 87:2750-2754, IDS). We respectfully disagree with the Examiner for the reasons that follow.

The Examiner relies on the recent Supreme Court Decision in KSR International Co. v. Teleflex Inc. (hereinafter "KSR") in supporting his conclusion of obviousness. KSR confirmed that "the combination of familiar elements according to known methods is likely to be obvious when it does more than yield predictable results". On that basis, the Examiner concludes on page 6 of the office action that "it is prima facie obvious to one the artisan to modify the method of Jaleco by substituting one stromal cell (S-17) with another OP-9 that is modified to express DL-1 with reasonable expectation of successfully achieving predictable result".

Applicant strenuously maintains their position that one of skill in the art would no way predict that OP-9 cells modified to express DL-1 or DL-4 would be useful in generating the claimed types of T cells. The decision in KSR reminds us to look to the three factual inquiries enunciated by the Court in Graham v. John Deere which are discussed in turn below.

1. Determine the Scope and Content of the Prior Art

The present invention is in the general area of generating T cells *in vitro*. At the time of the invention, it had been well established for decades that the thymus was required for generating T cells in culture. Accordingly, *in vitro* methods for generating T cells required an intact three-dimensional (3-D) thymic architecture such as the fetal thymus organ culture (FTOC) system (Hare et al., Semin. Immunol. 1999, 11: 3; Anderson et al., J. Immunol. 2008, 181: 7435). FTOC systems, while functional, are rather impractical and inefficient.

OP-9 stromal cells were known at the time of the invention to be useful in generating B cells and NK cells in culture. OP-9 cells are derived from bone marrow so their utility in this regard was not unexpected. At the time of the invention, OP-9 cells had not been used to generate T cells and had not been transformed to express DL-1 or DL-4.

S-17 stromal cells transformed with DL-1 were known to generate NK/T cell progenitors and a small minority population of double positive T cells. Such cells were unable to generate any mature T cells (Jaleco et al.).

2. Ascertain the Differences between the Claimed Invention and the Prior Art

The present invention relates to the unexpected finding that OP-9 stromal cells that are modified to express DL-1 or DL-4 can be used to form cells of the T cell linage by culturing stem cells or progenitor cells with the transformed OP-9 cells. Independent claim 12 specifies that the formed T cells are TCR-$\alpha\beta^+$ $CD4^-CD8^+$ T cells or TCR-$\gamma\delta^+$ T cells. Independent claim 22 relates to a method of expanding cells of the T cell lineage selected from one or more of the following lineages:

(i) $CD4^-$ $CD8^-$ $CD25^+$ $CD44^+$ double negative T cells;

(ii) $CD4^-$ $CD8^-$ $CD25^+$ $CD44^-$ double negative T cells;

(iii) TCR-$\alpha\beta^+$ $CD4^-$ $CD8^+$ T cells; and/or

(iv) TCR-$\gamma\delta^+$ T cells.

The Examiner is of the opinion that the Jaleco et al. reference is the closest prior art. The difference between Jaleco et al. and the present invention is that the present invention uses OP9 cells transformed with DL-1 or DL-4 and Jaleco et al. use S-17-DL-1 cells. Both untransformed OP-9 and S-17 are functionally similar in their ability to generate B cells. However, they are **unexpectedly** vastly different in their ability to generate T cells. Importantly, **Jaleco failed to produce any of the T cell phenotypes recited in the claims**.

3. Determine the Level of Ordinary Skill in the Art

The person of ordinary skill in the art is a person who would have been aware of the known FTOC system for generating T cells. The person would also be aware of the S-17 system described by Jaleco et al.

One of ordinary skill in the art would in no way predict that transformed OP-9 cells would be better at generating T cells than transformed S-17 cells. The Examiner suggests that Jaleco may have been able to generate T cells had they cultured the cells for a longer a duration of culture. Such a theory was also put forth in the concluding paragraphs of Jaleco et al. wherein they stated that "studies aimed at clarifying this issues are now underway". Jaleco et al. was published in 2001. One would expect that if they had conducted such studies and determined that T cells were in fact produced, such a study would have longed been published by now. A search of Pubmed demonstrates that Jaleco et al. has no further publications since the 2001 paper. Her supervisor Leonor Parriera, did publish a review article (copy enclosed) in 2003

discussing the role of Notch signaling in lymphopoiesis (Parriera et al. seminars in Immunology 15(2003) 81-89). The paper does not report any further success in generating T cells using S-17-DL1 cells.

We do not understand the Examiner's statement that "Applicants have neither rebutted nor provided evidence to demonstrate that condition that produces T cells of different lineage (cell type, incubation time, growth medium and other condition) on OP9-DL1 would not be produced under similar cells on S-17-DL1". In Example 9 of the present application, the inventors compared their system to Jaleco's system and demonstrated that under identical culture condition S-17-DL-1 cells were unable to generate any T cells other than a small population of double positive T cells. The claims do not include double positive T cells. Therefore, the inventors have shown that the system of Jaleco et al. can not produce the claimed types of T cells.

Applicant's understanding of the state of the art and the differences between the claimed invention and the prior art, is further supported in the attached review article by Lehar and Bevan published in 2002 (Lehar and Bevan. Immunity. Vol. 17, 689-692, 2002). The article confirms that Jaleco et al. "were unable to generate any mature T cells". The article goes on to state that the present inventors have developed "a previously unavailable, easily manipulable culture system that will undoubtedly facilitate future studies aimed at characterizing the signals required throughout this complex pathway differentiation" (emphasis ours).

In summary, Applicant maintains their position that the Examiner has failed to provide any reasoning as to why the use of OP-9 cells transformed with either DL-1 or DL-4 to generate T cells in vitro would be expected or predictable. In fact, the results provided in Jaleco et al. would teach away from the invention as they demonstrate that another type of stromal cell (S-17 cells) transformed with DL-1 were unable to generate any of the claimed T cells in culture.

We also note the Examiner has dismissed the evidence that Applicant provided regarding the inability of NIH3T3 cells, transformed with DL-1 or DL-4 to induce T-cells. We submit that the data is relevant as these cells do support B-cell development and therefore are analogous to untransformed OP9 cells as well as S-17 cells. The data supports our position that it is not predictable that a cell that supports B-cell development can be induced to support T cell development by transforming it with DL-1 or DL-4.

The deficiencies in Jaleco et al. are no way remedied by combining it with any one of Nakano et al.; Pui et al.; and Tatsumi et al. Nakano et al. is not concerned with preparing T cells. Nakano et al. uses untransformed OP9 cells to induce B cells, erythroid cells and myeloid cells. The Examiner asserts that Nakano "provided motivation to use OP-9 cells in particular, given desirable advantages that were well-known and accepted at the time of filing". At the time of filing, OP-9 cells were only known to induce B cell development. There would be no motivation to use these cells for T-cell development, especially based on the teachings of Jaleco et al. Jaleco teaches that a stromal cell line that is useful in stimulating B-cell development is not useful in inducing T-cells even when transformed with DL-1. There would be no basis for a person of skill in the art to then try another stromal cell line to achieve the present invention.

Tatsumi et al. is not relevant and it does not use modified stromal cells to produce mature T cells. While Tatsumi et al. teaches the generation of mature T cells, the precursor cells used in Tatsumi were not stem cells or progenitor cells as claimed in the present invention. Pui et al. discloses that Notch 1 plays a role in early lymphopoieisis. However, Pui does not discuss the Notch ligand DL-4 or DL-4 or the ability to generate T cells using OP-9 cells transformed with DL-1 or DL-4.

In summary there is nothing in the combined teachings of the prior art coupled with common general knowledge that would make the present claims obvious or predictable. As the Examiner is aware, after the KSR decision the USPTO released "Examination Guidelines for Determining Obviousness..." (Federal Register. Vol. 72, No. 195, Oct. 10, 2007). The Guidelines advise Examiners to resolve the Graham factors as discussed above. The Guidelines also state that there must be "some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness". Some of the rationales disclosed in the Guidelines are discussed below.

Simple Substitution

The substitution of S-17 cells for OP9 cells is clearly not a "simple substitution of one known element for another to obtain predictable results", (Examination Guidelines) as S-17 cells do not work in the generating the claimed T cells.

Obvious to Try

The invention was clearly not "obvious to try". The prior art did not provide "a finite number of identified, predictable solutions with a reasonable expectation of success" (Examination Guidelines). The art taught that S-17-DL1 cells did not work. In addition, there are hundreds of stromal cell lines and one of skill in the art could in no way predict that OP-9 cells transformed with DL-1 or DL-4 would be able to generate T cells in vitro.

Teaching, Suggestion, Motivation

As stated previously, there was no teaching, suggestion or motivation in the prior art that would have led one of skill in the art to the invention. On page 5 of the office action the Examiner states that the "recent KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness". We disagree as it is listed as a rationale in the Guidelines.

Secondary Considerations

Secondary considerations must also be considered when determining whether an invention is obvious. Secondary considerations include long felt but unsolved need in the art, failure of others and unexpected results (Guidelines). All three of these are present in the present invention.

The long felt but unsolved need in the art is evidenced in the fact that for decades the only system used to generate T cells in culture was the FTOC system, which is rather cumbersome and impractical. The present system is simple and efficient which is confirmed in the attached Lehar and Bevan article. The long felt need is also evidenced by the fact that many laboratories around the world have already obtained the OP9-DL1 cells and are now using them. Over the last six years, hundreds of material transfer agreements have been executed providing these cells to other research labs.

The failure of others is evidenced in the work by Jaleco et al., as they were unable to generate mature T cells using S-17 cells transformed with DL-1.

The unexpected results are evidenced in the examples of the present application, which demonstrate considerable expansion of T cells using OP-9-DL-1 cells. For example, a 15-20 fold expansion was observed by day 12 in culture. When transformed S-17 cells were cultured under the same conditions, no such expansion was observed.

On page 7 of the office action, the Examiner concludes that in "absence of any objective evidence or declaration the rejection is maintained". We have provided ample evidence above in support of the inventiveness of the claims. In addition, we enclose two declarations under 37 C.F.R. 1.132 by two independent experts in the field of the invention. The first declaration is by Charles Surh (hereinafter "the Surh declaration") who is a professor of Immunology at the Scripps Research Institute. Dr. Surh is a

leading authority on the immune system and the role of T lymphocytes. Dr. Surh believes that the art cited by the Examiner would not make the invention obvious. See item 4 of the Surh declaration. In fact Dr. Surh is of the opinion that the results reported in Jaleco et al. are "a great over interpretation of their results..." and that their data is not unequivocal proof of T cell development.

The second declaration is by Ellen Rothenberg (hereinafter "the Rothenberg declaration"). Dr Rothenberg is a Professor of Biology at the California Institute of Technology. Her research studies the molecular mechanisms that are responsible for T lymphocyte development. Dr. Rothenberg believes that the inventors' "method for T-cell development in vitro was nothing short of a revolution". See item 4 of the Rothenberg declaration. Dr. Rothenberg also confirms that the claimed method was clearly not obvious based on the cited prior art. She concludes that "the success of any attempt like that of the inventors was viewed at the time as highly unlikely on the basis of these three facts about the complex roles of Notch, the discontinuous, multistep nature of T-cell development, and the paradigm that 3-D organ structure was needed to induce and sustain T-cell development". See item 7 of the Rothenberg declaration.

In view of the foregoing, we respectfully request that all of the objections to claims under 35 USC § 103 be withdrawn.

At the interview, Examiner Bertoglio raised an issue regarding the phrase "cells capable of differentiation into cells of the T-cell lineage" found in claim 12. As discussed, the method of the invention is amenable to any cell that can be induced to differentiate into a T cell using the claimed method. In the application as filed the inventors demonstrated that the method works with a variety of cells that posses the potential to give rise to T cells, including fetal liver, bone marrow, human cord blood and embryonic stem cells. In addition, since the application was filed many groups have used the claimed method on many different types of stem/progenitor cells, including subsets

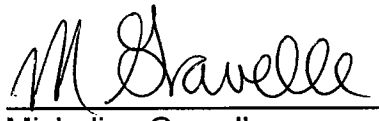
found in fetal liver, bone marrow, blood and thymus (reviewed in: de Pooter et al., Curr Opin Immunol 2007, 19:163 copy enclosed). Additionally, since the claimed method provides the means by which to ascertain whether a particular stem/progenitor cell type possess T cell lineage potential, it is then likely that any novel means to generate stem cells, such as induced-pluripotent stem (iPS) cells (Takahashi et al., Cell 2006, 126:663), could also form cells capable of differentiation into cells of the T-cell lineage.

The Commissioner is hereby authorized to charge any deficiency in fees (including any claim fees) or credit any overpayment to our Deposit Account No. 02-2095.

In view of the foregoing, we respectfully submit that the application is in order for allowance and early indication of that effect is respectfully requested. Should the Examiner deem it beneficial to discuss the application in greater detail, he is kindly requested to contact Micheline Gravelle by telephone at 416-957-1682 at his convenience.

Respectfully submitted,

Thomas M. Schmitt, et al.

By 

Micheline Gravelle
Reg. No. 40,261
Bereskin & Parr
Box 401, 40 King Street West
Toronto, Ontario
Canada M5H 3Y2
Tel: 416-957-1682
Fax: 416-361-1398